

October 10, 2013

Dear Colleagues,

At the Conference of the National Tuberculosis Controllers Association in June 2013, concerns were raised about adverse effects from the 12-dose regimen of directly-observed therapy (DOT) of once-weekly isoniazid-rifapentine (INH-RPT) in treating latent *Mycobacterium tuberculosis* infection (LTBI). I am writing to update you on what we are learning about this regimen. **In brief, the experience to-date shows that serious adverse effects associated with DOT INH-RPT are uncommon and similar to those that were observed during the controlled treatment trials.** At sentinel U.S. sites where DOT INH-RPT has been used under routine conditions, the completion of therapy has been 80% or more, notably greater than what has been typically achieved with 9 months of daily isoniazid. The Division of Tuberculosis Elimination (DTBE) is gathering information both from you and from ongoing clinical research that will inform future practices with DOT INH-RPT. As we gain more experience, we may need to reconsider how we select patients who should receive this regimen or how we monitor for adverse effects. **At present, the evidence does not support revisions to the current national guidance for DOT INH-RPT (CDC 2011 MMWR 60:1648-53).**

TB Trials Consortium (TBTC) Study 26 (PREVENT TB), compared DOT INH-RPT with self-administered therapy (SAT) of isoniazid for nine months (9H) for treatment of LTBI (Sterling et al., NEJM 2011, 365:2155). With approximately 4,000 participants in each treatment arm, this study found DOT INH-RPT to be as efficacious as SAT 9H in preventing TB, and more likely to be completed. No deaths were attributed to DOT INH-RPT. Fewer participants developed hepatotoxicity on DOT INH-RPT compared to SAT 9H (0.4% vs 2.7%). Similar proportions developed rash (0.8% vs 0.6%). However, more patients on DOT INH-RPT than on SAT 9H (3.8% vs 0.5%) developed reactions that were called “possible hypersensitivity,” and that presented with a diverse group of signs and symptoms including fever, chills, headache, fatigue, red eyes, dizziness, urticaria, pruritis, musculoskeletal pain, and/or petechiae. These conditions are similar to the rifamycin drug-associated reactions that were first described in older literature (e.g., Poole G, Potentially serious side-effects of high-dose twice-weekly rifampicin. Postgrad. Med. J. 1971, 47:742-747 and Girling DJ, Adverse reactions to rifampicin in antituberculosis regimens. J. Antimicrob. Chemother 1977, 3:115-132), and which have been observed rarely in association with all rifamycin drugs. Among Study 26 participants with the reactions, six patients also had systolic blood pressure of less than 90 mm Hg (0.15% or 1.5/1000 participants). Two other studies of the DOT INH-RPT regimen (conducted in Brazil and in South Africa) found that the regimen is effective, tolerable, and safe (Schechter et al, AJRCCM 2006;173:922 and Martinson et al, NEJM 2011;365:11). **Based on these findings, CDC recommends DOT INH-RPT as an equal alternative to the SAT 9H regimen for otherwise healthy patients aged 12 years or older who have LTBI and risk factors that are predictive of progression to TB disease. Monitoring for adverse events is also recommended. Serious adverse events should be reported to FDA and to CDC (CDC; MMWR 2011; 60:1648).**

In light of safety data from the studies above, particularly the reports of “possible hypersensitivity,” **CDC and its partners are monitoring the implementation and safety of the DOT INH-RPT regimen:** (1) TBTC Study 33 (the “iAdhere” study), a controlled trial comparing DOT INH-RPT with self-administration of the same INH-RPT regimen (SAT INH-RPT), (2) ongoing LTBI treatment surveillance for severe adverse events (i.e., hospitalization or death), (3) post-marketing sentinel site evaluation of DOT INH-RPT usage under program conditions, (4) in-depth evaluation of “possible hypersensitivity” reactions among Study 26 participants, (5) state health department evaluations of the DOT INH-RPT regimen (activities presented at the June NTCA meeting), and (6) collaboration with Sanofi, which manufactures Priftin[®] (rifapentine), to review animal toxicology data.

Discussion of adverse event reports related to DOT INH-RPT at the June 2013 NTCA meeting stimulated additional and updated assessments of the safety of the SAT INH-RPT arms in TBTC Study 33. Senior DTBE staff and representatives from the Study 33 protocol team met on July 2, 2013 by teleconference with the TBTC Data and Safety Monitoring Board (DSMB) to review updated Study 33 data by study arm. The same DTBE and TBTC staff met by teleconference on July 12, 2013, with the chair of the CDC IRB responsible for oversight of Study 33, a representative of the DSMB, two members of the TBTC Community Research Advisory Group (CRAG), CDC’s Associate Director for Science, the National Center for HIV/AIDS, Viral Hepatitis, STD, and TB Prevention Deputy Associate Director for Science, the protocol chairs for TBTC Studies 26 and 33, and project officers of the surveillance and sentinel site evaluation projects mentioned above. This second group considered whether the data suggested that the risk-benefit assessment for Study 33 should be revised; particular attention addressed the safety of patients allocated to the SAT INH-RPT arms. **The group determined that current information indicated that the original risk-benefit assessment for Study 33 was still valid. However, the discussants felt that additional education efforts would be desirable, to inform both healthcare providers and patients regarding the possible occurrence of hypotension or other serious adverse effects among patients taking intermittent rifamycin LTBI treatment regimens.**

To maximize patient safety, I would like to use this opportunity to remind you that **use of the DOT INH-RPT regimen**

- **is recommended as an equal alternative to SAT 9H for treating LTBI** in otherwise healthy patients aged ≥12 years who have LTBI and are at a high risk of developing TB;
- **should include administration by directly observed therapy (DOT) only;**
- **has been associated with potential side effects** of isoniazid and rifapentine, including signs and symptoms such as fever, headache, dizziness, musculoskeletal pain, petechiae, purpura, rash and pruritus, and, very rarely, hypotensive reactions;
- **should include clinical monitoring for all patients**, with at least monthly clinical assessment, including inquiries about side effects and a physical examination; although blood tests are not recommended for everyone, baseline and subsequent tests should be performed for certain patients (see MMWR 2011; 60 (No.48): page 1653 and MMWR 2000; 49 (No. RR-6): page 39);

- **should be accompanied by education of patients** about the symptoms and signs that can result as adverse effects of the drugs being prescribed, and about the need for prompt cessation of treatment and for clinical evaluation should symptoms occur (at each visit, patients on any LTBI regimen should be advised to stop therapy and immediately contact their providers upon the first sign or symptom of a possible adverse effect);
- **may be complemented with treatment counseling** using materials such as the CDC-created TLTBI Fact Sheets (available in English and Spanish) and Patient Education Brochure (available in English) on the CDC's TB internet website:
www.cdc.gov/tb/publications/factsheets/treatment.htm
www.cdc.gov/tb/esp/publications/factsheets/treatment.htm
www.cdc.gov/tb/publications/pamphlets/12-doseregimen.htm ;
- **may usefully include evaluation of concomitant medications** received by patients at each monthly evaluation. Once-weekly RPT (like other rifamycins) may induce increased metabolism of many medications, particularly those metabolized by cytochrome P450 isoenzyme 3A4. As a result, in the absence of more specific information about drug interaction, once-weekly INH-RPT should not be used with affected medications having narrow therapeutic ranges -- e.g., methadone, warfarin, oral contraceptives -- except with careful monitoring and/or adjustments.

Any serious adverse events¹ related to use of the DOT INH-RPT regimen should be reported to the U.S. Food and Drug Administration using the MedWatch Online Voluntary Reporting Form (see www.fda.gov/Safety/MedWatch/HowToReport/default.htm or call 1-800-FDA-1088). "Severe" adverse events (i.e., hospitalizations or deaths) associated with use of any LTBI regimen should be reported to CDC (e-mail: LTBIdrugevents@cdc.gov). Health providers should be asked to direct questions about the DOT INH-RPT regimen to their local or state TB programs, to any of the 5 Regional Training and Medical Consultation Centers, or to DTBE staff at CDC in Atlanta, as you best advise.

¹ For FDA's definition of "serious adverse event," see <http://www.fda.gov/Safety/MedWatch/HowToReport/ucm053087.htm>

In summary, the 12-dose DOT INH-RPT regimen for LTBI represents a significant advance in our efforts to prevent TB. Learning how to use the regimen optimally will require collaboration involving patients, providers, and TB program staff at local, state and federal levels. I encourage you to share the information in this letter with all who may employ this regimen, to assist us in our joint efforts to define how to use this promising new tool most effectively and safely.

Sincerely,



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Centers for Disease Control and Prevention

Attachment**Activities evaluating the implementation and safety of the DOT INH-RPT regimen**

1. Although TBTC Study 33 is designed primarily to evaluate adherence, the study includes enhanced safety data collection, specifically designed to characterize any “possible hypersensitivity” reactions more clearly than was possible in Study 26. As of September 27, 2013, 583 participants have been enrolled of 1,000 planned. DTBE is aware of anecdotal reports (R Belknap, personal communication) that 3HP is already being prescribed for self-administered use despite recommendations for DOT (CDC 2011); this reinforces the importance of Study 33.
2. Following the experience with the 2-month regimen of rifampin and pyrazinamide (2RZ), DTBE established a surveillance system for all **severe** adverse events (defined as hospitalization or death) occurring among patients on TLTB (MMWR 2003; 52:735; MMWR 2010; 59:224). As of September 23, 2013, this system has received 15 reports of hospitalizations of patients who were receiving DOT INH-RPT. All but one arose in the context of DTBE’s ongoing post-marketing evaluation of DOT INH-RPT (see item 3 below). Of the 15 reported events, 9 have been fully investigated on-site by DTBE personnel, 2 investigations are in progress, and 4 have been proposed for investigation on-site. No deaths have been reported. Liver injury has not been a prominent feature of these events. Hospitalizations have been brief, no major dermatological reactions have been reported, and no patient with hypotension has required vasopressors.
3. Active post-marketing surveillance of DOT INH-RPT is presently being conducted by CDC at 13 US sites. By May 27, 2013, 1,421 patients had started therapy. Of the 1,260 who had sufficient time, 1,051 (83%) had completed treatment. 117 (9%) stopped treatment because of symptoms or abnormal transaminase levels. Fourteen (1%) persons were hospitalized, and were reported to the severe adverse event surveillance project (see item 2 above). No deaths or long-term sequelae have been reported.
4. “Possible hypersensitivity” reactions, including hypotension, in TBTC Study 26 are receiving careful scrutiny by the study team. A panel of internationally recognized allergists has been consulted to assist in characterizing these events. As part of this analysis, one additional instance of hypotension was identified, for a total of 7 (0.18% or 1.8/1,000 participants) in TBTC Study 26. Data from Study 26 were presented at the March 2013 Conference on Retroviruses and Opportunistic Infections (CROI), at the May meeting of the American Thoracic Society (ATS), and at the June NTCA meeting. A manuscript describing the Study 26 events in detail is in preparation. Because these reactions are not believed to be

IgE-mediated, the allergist consultants advise that use of the term “hypersensitivity” may create confusion; an alternative descriptor is being considered.

5. Posters were presented at the NTCA meeting from Arkansas, Connecticut, Mississippi, and New Jersey that showed high completion rates for the DOT INH-RPT regimen. Adverse event rates and severity were similar to the Study 26 and the post-marketing project experience. Together, state TB control program abstracts described 1,137 starts of the DOT INH-RPT regimen (although many of these treatment starts are also included in CDC’s post-marketing surveillance project, #3 above).

6. Pharmacovigilance and other staff at Sanofi are cooperating with DTBE in these efforts.

NB: For those interested, links to earlier publications describing occurrence of “possible hypersensitivity” or “rifamycin-associated drug reactions” are provided below. It is important to note that these published reports often involve events occurring in the context of combination therapy with rifampicin and other anti-TB drugs, especially isoniazid.

<http://europepmc.org/articles/PMC2395744/pdf/bullwho00431-0054.pdf>

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1798649/pdf/brmedj02660-0035.pdf>

<http://informahealthcare.com/doi/pdfplus/10.1517/14740338.5.2.231>